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Original article

Molecular docking elucidates the plausible mechanisms underlying the anticancer properties of acetyldigitoxigenin from *Adenium obesum*

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ABSTRACT

Adenium obesum (Forssk.) Roem. & Schult. is a promising medicinal plant belonging to the Apocynaceae family. It is a rich source of various phytochemicals such as cardiac glycosides, flavonoids, terpeniods, pregnanes etc. which have different pharmacological properties such as anticancer, antibacterial, acaricidal etc. While previous reports showed the anticancer activity of the aerial parts of the plant extract of *A. obesum*, the mechanisms of action of its chemical constituents are not known. The present study is aimed at elucidation of plausible mechanisms of anticancer activity of the plant by evaluating the binding interaction of its nine major selected compounds with macromolecular receptors implicated in the initiation and progression of cancer using various *in silico* approaches. Molecular docking results showed that the compound Δ^{16}-3-Acetyldigitoxigenin (16-anhydro-3-acetylgitoxigenin) scored the best binding energy scores with the majority of the target proteins. The molecular binding of the compound was stabilized through hydrogen bonds as well as hydrophobic interactions, and also possesses favorable drug-like properties without significant toxicities.

1. Introduction

Every year, approximately 6.7 million deaths take place around the world due to various types of cancer (ACS, 2020). A wide array of cytotoxic agents and radiotherapy used in the cancer treatment have limitations in their usage e.g. side effects, and efficacy (Kim et al., 2007; Stopeck and Thompson, 2012); therefore, the development of better effective therapeutics for the cancer treatment from natural products remain continues because of its minimal side effects (Da Rocha et al., 2001; Vermani and Garg, 2002; Gurib-Fakim, 2006).

Although *Adenium obesum* (Forssk.) Roem. & Schult. (family Apocynaceae, commonly known as 'Desert Rose') is primarily an ornamental poisonous plant, the whole plant including latex has been used in traditional system of medicines for the treatment of various aliments e.g. skin lumps, wound, ear ache, rhinitis, gonorrhea and infectious diseases. It contains nearly 50 major chemicals constituents belonging to the class of cardenolides, flavonoids, pregnanes and triterpenes (Versiani et al., 2014). The recent reports (Almehdar et al; 2012; Hossain et al., 2017; Ali et al., 2019a,b) established the anticancer activity of extract of aerial part of *A. obesum* but the modes of action of the chemical constituents have not been understood; therefore, the aim of the current study is to elucidate the plausible molecular mechanisms underlying the anticancer activity of *A. obesum* extract using *in silico* approaches.

2. Materials and methods

2.1. Preparation of ligand and receptor

The structures of nine major compounds of *A. obesum* (Table 1) were modeled using Chemsketch. The three-dimensional structures of selected macromolecular receptors e.g. (i) CDK-2 [PDB ID: 1DI8], (ii) CDK-6 [PDB ID: 1XO2], (iii-iv) Topoisomerases-I [PDB ID: 1T8I] and II [PDB ID: 1ZXM], (v) BCL-2 [PDB ID: 2O2F],

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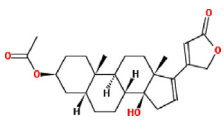
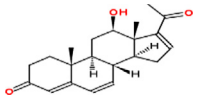
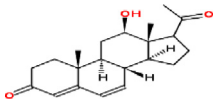
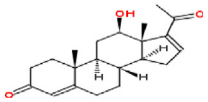
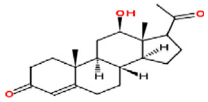
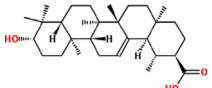
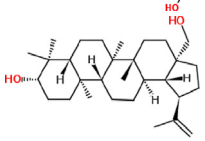
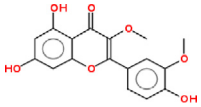
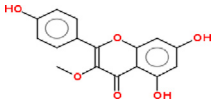
Table 1
The major compounds derived from *A. obesum* selected for molecular docking.

Compounds	Name	Structure	Class	Parts	References
1	Δ^{16}-3-Acetyldigitoxigenin (16-anhydro-3-acetylgitoxigenin)		Cardiac glycosides	Stem	Vethaviyasar and John (1982)
2	12β-Hydroxypregna-4,6,16-triene-3,20-dione (neridienoneA)		Pregnanes	Stem, roots, leaves	Yamauchi and Abe (1990) Nakamura et al. (2000)
3	12β-Hydroxypregna-4,6-diene-3,20-dione (16,17-dihydroneridienone A)		Pregnanes	Stem, roots, leaves	Yamauchi and Abe (1990) Nakamura et al. (2000)
4	12β-Hydroxpregna-4,16-diene-3,20-dione		Pregnanes	Leaves	Nakamura et al. (2000)
5	12β-Hydroxypregn-4-ene-3,20-dione		Pregnanes	Leaves	Nakamura et al. (2000)
6	Dihydroifflaionic acid		Triterpenoids	Aerial	Hoffmann and Cole (1977)
7	Lup-20(29)-ene-3,28-diol (betulin)		Triterpenoids	Stem bark	Tijjani et al. (2012)
8	Quercetin 3,3′-dimethyl ether		Flavonoids	Aerial	Hoffmann and Cole (1977)
9	Kaempferol 3-methyl ether		Flavonoids	Aerial	Hoffmann and Cole (1977)

(vi) VEGFR-2 [PDB ID: 2OH4], and (vii) Telomere: G-quadruplex [1L1H] were retrieved from Protein Data Bank (PDB). The 3-D structures of ligands optimized with MMFF94 force field (Halgren, 1996), and the receptors prepared following our previously described method (Gurung et al., 2016) were used to execute docking. The binding sites were defined by choosing grid boxes of suitable dimensions around the bound co-crystal ligands.

2.2. Molecular docking

The Lamarckian Genetic Algorithm was used for performing molecular docking using AutoDock4.2 (Morris et al., 2009) considering the docking parameters from our previously described method (Gurung et al., 2016). A total number of 50 independent docking runs were performed for each ligand. The conformations were grouped under clusters by considering a difference of less than 2.0 Å of root mean square deviation (RMSD). The lowest free energy of binding (ΔG) and the lowest inhibition constant (K_i) were considered for choosing the most favorable binding pose. The molecular interactions between the compounds and receptors were studied using LigPlot + v 1.4.5 (Laskowski and Swindells, 2011).

2.3. Validation of docking method

In order to check the suitability of molecular docking parameters and algorithm to reproduce the native binding poses, redocking experiment was performed using the co-crystal ligands.

2.4. Determination of physicochemical properties of the compounds

DataWarrior program version 4.6.1 was used for the determination of various physicochemical properties of the selected compounds such as drug likeness and toxicity (Sander et al., 2015).

3. Results and discussion

The three dimensional structure of nine major compounds [Δ16-3-Acetyldigitoxigenin (16-anhydro-3-acetylgitoxigenin), 12β-Hydroxypregna-4,6,16-triene-3,20-dione (neridienoneA), 12β-Hydroxypregna-4,6-diene-3,20-dione (16,17-dihydroneridienone A), 12β-Hydroxpregna-4,16-diene-3,20-dione, 12β-Hydroxypregn-4-ene-3,20-dione, Dihydroifflaionic acid, Lup-20(29)-ene-3,28-diol (betulin), Quercetin 3,3′-dimethyl ether, Kaempferol 3-methyl ether] from *A. obesum* were modeled and optimized. The optimized structures were used further for molecular docking studies (Table 1). Before performing molecular docking studies, we validated the docking protocol and algorithm through redocking experiment. In all the cases, the root mean square deviation (RMSD) between the docked and native co-crystal position were found to be less than 2 Å. This indicates that the docking protocols, and parameters employed in the present study can reliably predict the native conformations of the compounds (Januar et al., 2012).

Table 2
The binding energies and inhibition constants of selected compounds derived from *A. obesum* docked against molecular targets.

Compounds	Drug targets (PDB Entries)													
	CDK-2 (1DI8)		CDK-6 (1XO2)		Topoisomerase-II (1ZXM)		BCL-2 (2O2F)		VEGFR-2 (2OH4)		Telomere: G-quadruplex (1L1H)		Topoisomerase-I (1T8I)	
	BE (kcal/mol)	K_i(nM)	BE (kcal/mol)	K_i(nM)	BE (kcal/mol)	K_i(nM)	BE (kcal/mol)	K_i(nM)	BE (kcal/mol)	Ki(nM)	BE (kcal/mol)	K_i(nM)	BE (kcal/mol)	K_i(nM)
1	−11.39	4.50	−8.93	282.69	−11.45	4.03	−8.47	618.23	−10.17	35.14	−5.61	77,660	−10.94	9.49
2	−10.10	39.54	−10.11	39.13	−9.05	231.69	−8.23	923.49	−9.74	73.07	−7.55	2940	−9.13	201.63
3	−10.01	46.25	−9.99	47.72	−8.96	268.59	−8.23	933.55	−9.21	177.53	−7.30	4470	−9.34	143.28
4	−10.06	42.53	−9.96	49.96	−8.98	262.49	−8.24	905.38	−8.73	401.36	−7.38	3920	−9.81	64.68
5	−9.98	48.73	−10.03	44.34	−8.84	333.04	−8.37	736.14	−9.29	154.49	−7.43	3570	−9.69	78.71
6	−11.20	6.20	−6.02	38,380	−7.95	1490	−8.55	540.37	−8.41	679.17	−6.26	25,950	−9.82	63.21
7	−10.30	28.15	−6.43	19,240	−9.40	129.67	−8.73	400.37	−7.97	1430	−7.35	4100	−9.65	85.11
8	−8.30	819.79	−9.20	181.34	−7.42	3640	−5.95	43.29	−9.11	211.74	−8.92	287.67	−9.03	240.57
9	−7.74	2110	−9.05	232.35	−7.20	5280	−6.05	36,840	−8.69	426.31	−8.46	628.78	−8.61	487.63
Co-crystal ligand	−8.04	1270	−8.26	882.71	−11.11	7.24	−11.01	8.56	−12.46	0.738	−11.97	1.68	−10.75	13.23

The results of molecular docking are shown in Table 2. It is evident that compound 1 [(Δ^{16}-3-Acetyldigitoxigenin (16-anhydro-3-acetylgitoxigenin)] was best docked to CDK-2 with ΔG of −11.39 kcal/mol and K_i of 4.50 nM, which is significantly lower than the co-crystal ligand having ΔG of −8.04 kcal/mol and K_i of 1270 nM. LigPlot + results as shown in Fig. 1 indicates that the compound 1 was able to establish four hydrogen bonds through Lys33, Leu83 and Lys89. Further, this binding was strengthened by hydrophobic interactions with Ile10, Val18, Ala31, Val64, Phe80, Glu81, Phe82, His84, Gln85, Asp86, Leu134, Ala144, Asp145 and Leu148.

The compound 2 [12β-Hydroxypregna-4,6,16-triene-3,20-dione (neridienoneA)] was best docked to CDK-6 with a binding energy of −10.11 kcal/mol and K_i of 39.13 nM, which is much lower than

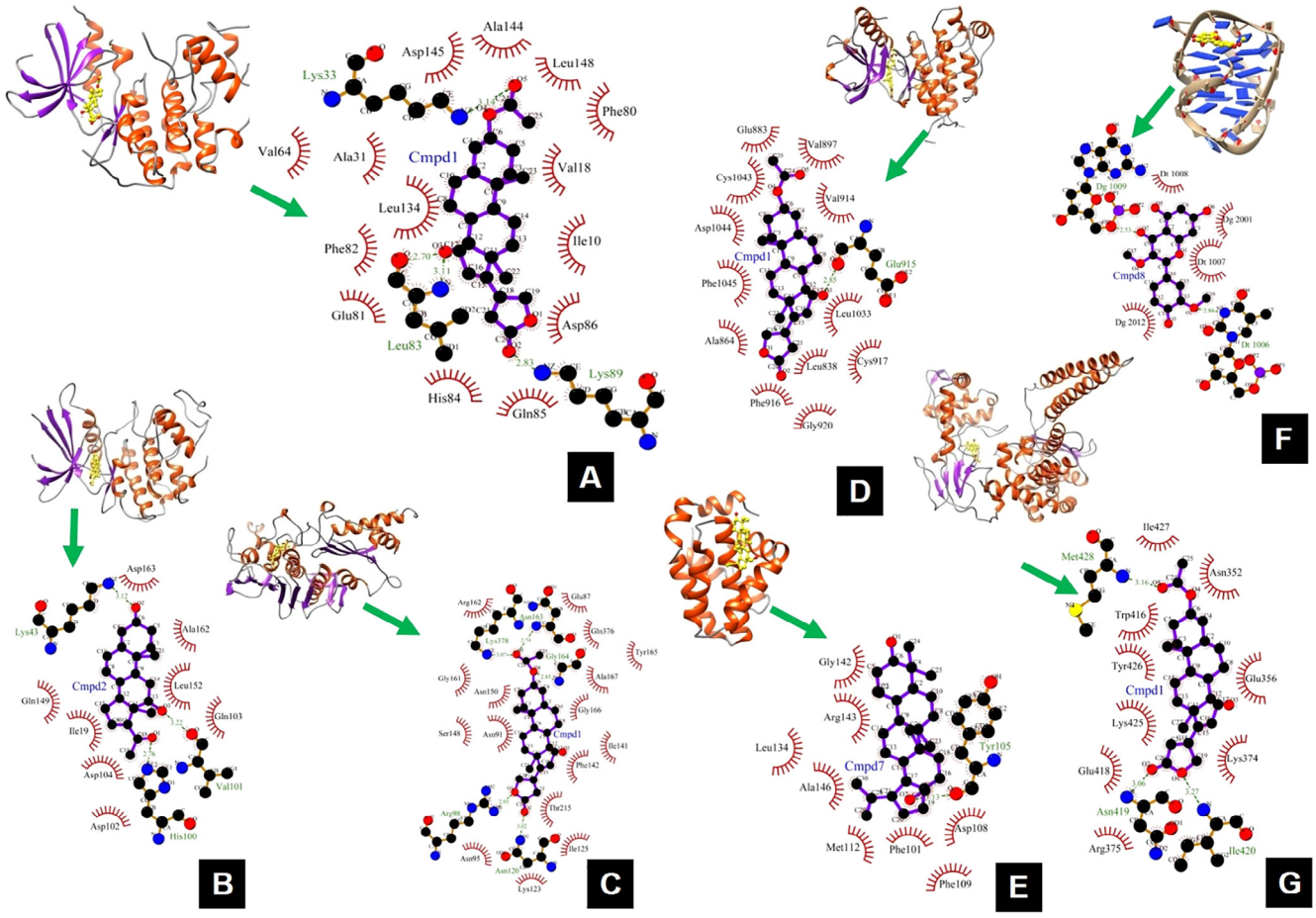


Fig. 1. The binding modes and LigPlot + results for receptor-ligand interactions. The molecular interaction between: CDK-2 and Δ^{16}-3-Acetyldigitoxigenin (16-anhydro-3-acetylgitoxigenin) (A); CDK-6 and 12β-Hydroxypregna-4,6,16-triene-3,20-dione (neridienoneA) (B); Topoisomerase-II and Δ^{16}-3-Acetyldigitoxigenin (16-anhydro-3-acetylgitoxigenin) (C); BCL-2 and Lup-20(29)-ene-3,28-diol (betulin) (D); VEGFR-2 and Δ^{16}-3-Acetyldigitoxigenin (16-anhydro-3-acetylgitoxigenin) (E); Telomere: G-quadruplex and Quercetin 3,3′-dimethyl ether (F); Topoisomerase-I and Δ^{16}-3-Acetyldigitoxigenin (16-anhydro-3-acetylgitoxigenin) (G). The hydrogen bonds are represented by green dashed lines with the bond distance. The residues contributing to the hydrophobic interactions are indicated with red arcs with spikes.

the co-crystal ligand having binding energy −8.26 kcal/mol and K_i of 882.71 nM. It formed three hydrogen bonds with Lys43, His100, Val101 and residues involved in hydrophobic interactions include Ile19, Asp102, Gln103, Asp104, Gln149, Leu152, Ala162 and Asp163. Again, compound 1 [(Δ^{16}-3-Acetyldigitoxigenin (16-anhydro-3-acetylgitoxigenin)] was found to be best docked to Topoisomerase-II with a binding energy of −11.45 and K_i of 4.03 nM which is slightly lower than the co-crystal ligand having a binding energy of −11.11 kcal/mol and K_i of 7.24 nM. It formed five hydrogen bonds with Arg98, Asn120, Asn163, Gly164 and Lys378 and hydrophobic interaction with residues Glu87, Asn91, Asn95, Lys123, Ile125, Ile141, Phe142, Ser148, Asn150, Gly161, Arg162, Tyr165, Gly166, Ala167, Thr215 and Gln376.

The best docked compound for BCL-2 was found to be compound 7 [Lup-20(29)-ene-3,28-diol (betulin)] with a binding energy of −8.73 kcal/mol and K_i of 400.37 nM which was found to higher than the co-crystal ligand with a binding energy of −11.01 kcal/mol and K_i of 8.56 nM. It was able to establish only one hydrogen bond with Tyr105 and hydrophobic interactions with residues Phe101, Asp108, Phe109, Met112, Leu134, Gly142, Arg143 and Ala146. Compound 1 [(Δ^{16}-3-Acetyldigitoxigenin (16-anhydro-3-acetylgitoxigenin)] was also best docked to VEGFR-2 with a binding energy of −10.17 kcal/mol and K_i of 35.14 nM which was found to be higher than the co-crystal ligand with binding energy of −12.46 kcal/mol and K_i of 0.738 nM. It showed good interaction with VEGFR-2 through one hydrogen bond with residue Glu915 and hydrophobic interaction via residues Leu838, Ala864, Glu883, Val897, Val914, Phe916, Cys917, Gly920, Leu1033, Cys1043, Asp1044 and Phe1045.

The best docked ligand for Telomere:G-quadruplex was compound 8 [Quercetin 3,3′-dimethyl ether] with a binding energy of −8.92 kcal/mol and K_i of 287.67 nM which was significantly higher than the co-crystal ligand with a binding energy of −11.97 kcal/mol and K_i of 1.68 nM. Compound 8 [Quercetin 3,3′-dimethyl ether] formed two hydrogen bonds with bases DT1006 and DG1009 and hydrophobic interactions via bases Dt1007, Dt1008, Dg2001 and Dg2012. Compound 1 [(Δ^{16}-3-Acetyldigitoxigenin (16-anhydro-3-acetylgitoxigenin)] is also best docked to Topoisomerase-I with a binding energy of −10.94 kcal/mol and K_i of 9.49 nM which is slightly lower than the co-crystal ligand with a binding energy of −10.75 kcal/mol and Ki of 13.23 nM. It formed three hydrogen bonds with Asn419, Ile420, Met428 and hydrophobic interactions via residues Asn352, Glu356, Lys374, Arg375, Trp416, Glu418, Lys425, Tyr426 and Ile427.

The physicochemical properties of the docked compounds are tabulated in Table 3. The majority of the compounds obeyed the Lipinski's rule of five (ROF) (Lipinski, 2004) except for compounds 6 [Dihydroifflaionic acid] and 7 [Lup-20(29)-ene-3,28-diol (betulin)] which showed one violation as their cLogP values were higher than the permissible limits. Compounds 1 [(Δ^{16}-3-Acetyldigitoxigenin (16-anhydro-3-acetylgitoxigenin)], 6 [Dihydroifflaionic acid], 7 [Lup-20(29)-ene-3,28-diol (betulin)], 8 [Quercetin 3,3′-dimethyl ether] and 9 [Kaempferol 3-methyl ether] were found to be non-mutagenic, non-tumorigenic, non-irritant and without any adverse effects on reproductive health. Compounds 2 [12β-Hydroxypregna-4,6,16-triene-3,20-dione (neridienoneA)], 3 [12β-Hydroxypregna-4,6-diene-3,20-dione (16,17-dihydroneridienone A)], 4 [12β-Hydroxpregna-4,16-diene-3,20-dione] and 5 [12β-Hydroxypregn-4-ene-3,20-dione] also showed similar results except for their possible toxicity on reproductive health. The majority of the compounds showed a good drug likeness score except for compounds 1 [Δ^{16}-3-Acetyldigitoxigenin (16-anhydro-3-acetylgitoxigenin)], 6 [Dihydroifflaionic acid] and 7 [Lup-20(29)-ene-3,28-diol (betulin)] which exhibited negative drug likeness score. The other physicochemical properties such as topological surface area (TPSA) and number of rotatable bonds (RB) were also found to be within permissible limits (TPSA $\leq$ 140 Å^2 and RB $\leq$ 10).

Thus, the present molecular docking studies revealed structural insights into possible binding modes of major active compounds of *A. obesum*, and identified the best docked compound for each target. The compound 1 (16-anhydro-3-acetylgitoxigenin) was found to be best docked (showed a high binding affinity, good number of hydrogen bonds and hydrophobic interactions with their respective molecular targets which play a key role in the pathogenesis of cancer) to four targets CDK-2, Topoisomerase-II, VEGFR-2 and Topoisomerase-I whereas Compound 2 (12β-Hydroxypregna-4,6,16-triene-3,20-dione), Compound 7 (Lup-20(29)-ene-3,28-diol) and Compound 8 (Quercetin 3,3′-dimethyl ether) were found to be best docked to CDK-6, BCL-2 and Telomere:G-quadruplex respectively with favorable drug-like properties; and thus, these compounds can be promising leads for the design of specific target inhibitors which would help with management of the disease.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Table 3
The physicochemical properties of the compounds derived from *A. obesum* [- (none), h (high)].

Compounds	Mol weight	cLogP	cLogS	HBA	HBD	TPSA	Drug likeness	Mutagenic	Tumorigenic	Reproductive Effective	Irritancy	Rotatable Bonds
1	414.54	3.3025	−4.414	5	1	72.83	−0.27262	–	–	–	–	3
2	326.434	2.787	−3.651	3	1	54.37	1.9744	–	–	h	–	1
3	328.45	2.8915	−3.915	3	1	54.37	1.9131	–	–	h	–	1
4	328.45	3.0624	−3.879	3	1	54.37	1.9189	–	h	h	–	1
5	330.466	3.1669	−4.143	3	1	54.37	1.8595	–	–	h	–	1
6	456.708	6.0021	−6.111	3	2	57.53	−2.3517	–	–	–	–	1
7	442.725	6.7202	−6.296	2	2	40.46	−23.933	–	–	–	–	2
8	331.299	0.8411	−2.164	7	3	113.29	1.5726	–	–	–	–	3
9	301.273	0.9111	−2.146	6	3	104.06	1.5726	–	–	–	–	2

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